



Metamizole: Current Status of the Safety and Efficacy

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SUMMARY

Metamizole is a nonsteroidal anti-inflammatory drug, with analgesic, antipyretic, spasmolytic, and weak anti-inflammatory properties. The analgesic effect of metamizole seems to be based on the inhibition of cyclooxygenase enzyme activity and stimulation of cannabinoid receptors. Its use is still controversial, mainly due to agranulocytosis, metamizole-induced serious adverse reaction. While in many countries it is withdrawn from the market, in some countries metamizole is available as a medication prescribed for strictly defined indications, while in the others like Mexico, Brazil and China it can be obtained as an Over-The-Counter drug. The most common adverse effects of metamizole are the skin and subcutaneous tissue disorders. Metamizole appears to be of similar efficacy to analgesics which are frequently used in the treatment of moderate to severe postoperative pain.

Keywords: metamizole, adverse drug reaction, agranulocytosis, pain, efficacy

INTRODUCTION

Metamizole is a nonsteroidal anti-inflammatory drug (NSAID), with analgesic, antipyretic, spasmolytic, and weak anti-inflammatory effects which belongs to the pyrazolones [1, 2]. It is a nonnarcotic analgesic with N02BB02 Anatomical Therapeutic Chemical code [3], which can be used orally and parenterally to prevent or treat pain of various origin and intensity, such as postoperative pain, acute injury pain, cancer and colic pain, as well as migraine [1-3].

MATERIALS AND METHODS

A general search strategy was developed to conduct the PubMed, Google Scholar, Scopus, Web of Sciences, Embase, and SCIndex search to identify all studies describing the safety and efficiency of metamizole. The reference sections of identified original studies and review articles were examined to determine other potentially relevant original studies that were not identified by the primary search.

The following key words were used: metamizole, safety, adverse drug reaction, ad-

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verse event, agranulocytosis, pain, efficacy and NSAID. After that, the relevant papers are included in this review.

In our paper, we used the data obtained from EudraVigilance database (<https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance>) and report of Medicines and Medical Devices Agency of Serbia (<https://www.alims.gov.rs/eng/>).

The aim of our study was to show up current status of the metamizole safety and efficacy, as well as pharmacokinetics characteristics, indication for use and worldwide availability of metamizole.

TOPIC

Mechanism of action

Metamizole achieves effects by central and peripheral mechanisms [4], but the exact mechanism of its analgesic effect remains partially unclear [2]. The analgesic effect of metamizole seems to be based on the inhibition of cyclooxygenase (COX) enzyme activity, predominantly COX enzyme type 2 [1]. Also, this is the base for its antipyretic effects [5, 6]. There is the an assumption that metamizole might be an inhibitor of the COX-3 isoenzyme, which thereby reduces prostaglandin synthesis in the dorsal horn of the spinal cord [7]. It seems that metamizole also acts by stimulation of cannabinoid receptors; as naloxone blocks the analgesic effect of metamizole, the interaction with the endogenous opioid system is proposed as one of the possible mechanisms for its analgesic properties [8, 5]. On the other hand, its weak anti-inflammatory activity, is possible due to the low affinity for COX in environments that are high in peroxide, such as inflamed tissues [9]. It has also been reported that metamizole has a dose-dependent effect on platelet aggregation through the inhibition of TXA₂ synthesis in platelets [10]. It also possesses a distinctive spasmolytic effect on the smooth muscles [10].

Pharmacokinetics characteristics

When it is administered orally, metamizole is rapidly hydrolysed to 4-methylaminoantipyrine (MAA), in gastric juice and this form is completely absorbed. The bioavailability of MAA was 85% for the tablets, 89% for the

drops, 54% for the suppositories and 87% for the intramuscular injection [11].

Metamizole is metabolized in the liver, and flavin monooxygenases are involved in this process [12]. The 4 major metabolites of metamizole are MAA, 4-amino-antipyrine (AA), 4-acetyl-amino-antipyrine (AAA) and 4-formyl-amino-antipyrine (FAA) [11, 12]. None of them binds significantly to plasma proteins (57.6% MAA, 47.9% AA, 17.8% FAA i 4.2% AAA). The volume of distribution after intravenous use in healthy volunteers was 33 L. Plasma concentration half-life of metamizole is similar for MAA, AAA and FAA in both slow and rapid acetylators. It is possible that impaired hepatic metabolism largely contributes to the prolonged MAA elimination in the elderly. All major metabolites of metamizole passage into the cerebrospinal fluid [10, 11]. The transfer of metamizole metabolites to breast milk was determined. After the intravenous use, more than 90% of drug is eliminated by urine, and less than 10% is eliminated by feces. Forty-eight hours after drug administration, MAA and AA were undetectable and FAA and AAA were represented in negligible concentration [11].

Clinical efficacy of metamizole

There are many studies [13] which have compared analgesic efficacy of metamizole with other analgesics. Single dose metamizole appears to be of similar efficacy to analgesics which are frequently used in the treatment of moderate to severe postoperative pain [13].

Authors Derry et al., in their meta-analysis, compared analgesic effect of single dose of metamizole, administered *per os* or intravenously (*i.v.*), with other analgesics (reference). They concluded that single 500 mg dose of metamizole has similar efficacy as 400 mg of ibuprofen, administered *per os*, while single 2.5 g dose of metamizole given *i.v.* is equivalent with tramadol, administered in doses of 100 mg, *i.v.* Metamizole is more effective than paracetamol given in dose of 1000 mg. [14].

Metamizole in dose of 1 g *versus* ibuprofen given in a single dose of 600 mg showed similar therapeutic effect while 2g of metamizole were superior to 600 mg of ibuprofen administered in patients who had undergone extraction of the lower third molar [15].

Rawal et al. compared the efficacy of analgesics given in tablet formulations: trama-

dol in dose of 100 mg every 6 h; 1 g of metamizole every 6 h, and 1 g of paracetamol every 6 h in the patients who underwent ambulatory hand surgery with regional anesthesia. Tramadol was the most effective analgesic with the highest incidence of side effects. Metamizole and paracetamol provided good analgesia with a decreased incidence of side effects in comparison with tramadol [16].

Schug et al. researched the role of non-opioids for postoperative pain and concluded that repeated doses of metamizole, up to 4 g per 24 h were identical in efficacy to 4 g of paracetamol given *i.v.* after breast surgery [17].

Authors Ohnesorge et al. conducted a randomized, double-blind, placebo-controlled study, comparing the effects of paracetamol and metamizole, administered *i.v.* with a placebo in patients after mastectomy. These analgesics and a placebo were administered 20 minutes before the end of the surgical procedure, as well as 4, 10 and 16 h after it. The intensity of post-operative pain in the metamizole-treated group and in the placebo-treated patients was similar, while in the paracetamol-treated group it was lower in the first postoperative hour. In the second postoperative hour, the intensity of the pain was lower than 2.5 (assessment has been done with numerical scale) in all groups. The authors concluded that paracetamol showed better efficacy in comparison with metamizole, and the repeated administration of metamizole in the form of short-term *i.v.* infusion was not effective for the treatment of postoperative pain after mastectomy [18]. The explanation could be found in the pharmacokinetic characteristics of metamizole and the route of administration. Namely, it is assumed that a short time *i.v.* infusion does not achieve sufficient concentration of the active metabolite MAA (2.5-7.5 times faster excretion of MAA was recorded after *i.v.* injection than after oral drug administration) [18].

Metamizole use during pregnancy and in pediatric population

In many countries (German, Spain, Brazil) metamizole is also available for the use in pediatric population. In children, recommended doses are 15-20 mg/kg, *per dosis*. Oral formulation of metamizole in doses of 500 mg/ml, as infant drops, is available in Brazil [19]. In Germany, it is present on the market as infant

drops (500 mg/ml), for children aged up to 3 months and who weigh more than 5 kg, as well as in tablets form for children older than 10 years [20]. In our country metamizole is subjected to marketing authorization for persons older than 18 years, while in Croatia it is assigned for older than 15 years [2, 21]. Based on the research which is conducted by Fieler et al., one dose of metamizole used for postoperative pain treatment in 1177 children aged up to 6 years was characterized as safe and tolerable [22].

The findings about teratogenic potential of metamizole are insufficient. In one of the studies the rate of congenital abnormalities in the metamizole group did not differ significantly from the rate in the paracetamol group. In the other study the connection between metamizole and diafragmal defects, cardiovascular abnormalities and other defects was established, in comparison with the control group [23]. Due to the insufficient data regarding the use of this drug in pregnancy, a study was conducted and data was reported by 555 pregnant women, in 2009, in Brasil. That was the first prospective study analyzing the teratogenic effect of metamizole in Latin America and was of great importance since its outpatient use is widespread and unrestricted. The data were obtained directly from the pregnant women or from their medical records or the antenatal notes. Based on this research, data have been obtained suggesting that metamizole use during pregnancy does not present any teratogenic risk and is not associated with intrauterine death, preterm birth, or low birth weight [23].

Metamizole is not licenced for use during pregnancy and lactation in Serbia, while it is allowed for use during the second trimester of pregnancy, under medical supervision in Croatia [2, 21].

Adverse reactions to metamizole

The most serious adverse effect of metamizole is agranulocytosis, which was the reason for withdrawal of this drug in many countries. Agranulocytosis (neutrophil count of less than $5 \times 10^9 \text{ L}^{-1}$) is a hematologic syndrome of acute onset in which the number of circulating neutrophils decreases, leading to a markedly increased susceptibility to bacterial infection, serious local infection or sepsis. Typical signs of agranulocytosis are inflammation of the

mucosa, sore throat, fever, increased erythrocyte sedimentation without or with only slight lymph node enlargement [13, 24]. They can appear from several days to up to 3 months after introducing metamizole into therapy. The risk of agranulocytosis seems to increase with duration of use, and it disappears 10 day after the last dose [25]. In the other hand, published epidemiologic studies have indicated a relatively low excess risk associated with short-term use of metamizole. The risk of agranulocytosis related to long-term use is still insufficiently clearly estimated [26]. Due to the same reason, metamizole was withdrawn from use in 1970s in USA. It was established that metamizole has similar chemical structure as antipirine, which was already indentified as provocator of agranulocytosis. There was cross over alergic reaction between antipirin and metamizole and therefore it was assumed that incidence agranulocytosis caused by metamizole was the same as for antipirine, so it was considered that the risk was one per 120 treated patients, based on prejudice, published and unpublished series of cases.

The international epidemiological study of agranulocytosis and aplastic anemia, organized by the metamizole manufacturers, showed that the overall annual incidence of agranulocytosis was 4.4 cases per million users (6.2 including hospital cases), with an annual mortality rate of 0.4 per million users [27]. The other recent study has concluded that the use of metamizole is associated with an estimated risk of agranulocytosis accounted 0.56 cases per million users [1]. Moreover, extensive epidemiological investigations showed that short-term exposure to metamizole does not increase the risk of agranulocytosis. This risk is lower than risk for aplastic anemia related to the application of indometacine or diclofenac [8].

In addition, the incidence of metam-

izole-induced agranulocytosis has varied geographically [13]. In some countries as Bulgaria, the risk of metamizole-induced agranulocytosis was astimated as very low (0.037 to 1 million persons), in Greece one case per 133,000-466,000 treatments, while in others such as Sweden (approximately 1:31,000 metamizole-treated inpatients and 1:1400 metamizole-treated outpatients) and the USA (0.79-0.86%, with a mortality rate of 0.57%) the incidence was high [13, 28]. Studies over the last few years from Spain, Switzerland, Germany, Poland and Latin America have pointed to the rarity of this serious adverse effect of metamizole therapy [28].

Metamizol causes agranulocytosis by immunological mechanisms, and specific human leukocyte antigen or HLA alleles may confer the risk [8, 28]. Also it is believed that repeated intravenous injections of metamizole might be directly toxic for granulocyte precursors [8]. In imune-mediated agranulocytosis, the drug or a metabolite binds irreversible to the neutrophil membrane. In the toxic reaction, the drug directly damages the myeloid precursor cells [29].

Several factors may affected on mortality caused by agranulocytosis, such as the length of application, general condition of the patient, treatment with effective spectrum antibiotics and/or Granulocyte Colony Stimulating Factor or G-CSF [30]. Analgetics which also can induce agranulocytosis are indometacin, oksifenbutazon and fenilbutazon. All adverse reactions to pyrazolones are not dose-dependent [31]. Also metamizol-induced hemolytic anemia and aplastic anemia have been reported [13].

It is interesting to note that the first bone marrow transplantation in the former Yugoslavia was performed in the patient with agranulocytosis as ADR of metamizole [32].

Based on the data from EudraV-

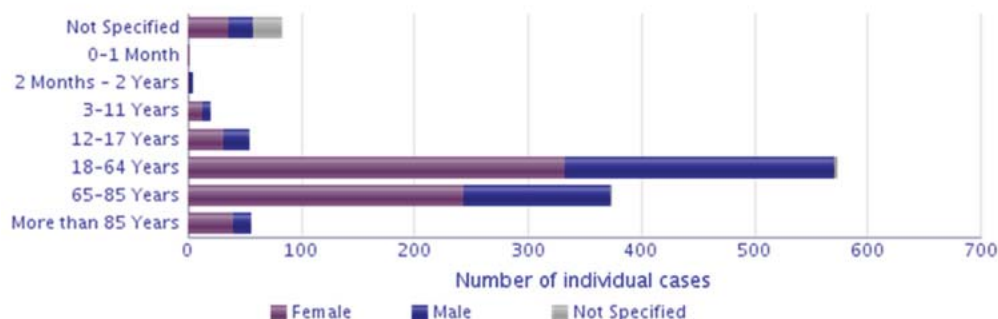


Figure 1. Distribution of individual cases of metamizole-induced agranulocytosis according by the patient age group

Figure 2. Distribution of individual cases of metamizole-induced agranulocytosis according by their outcome

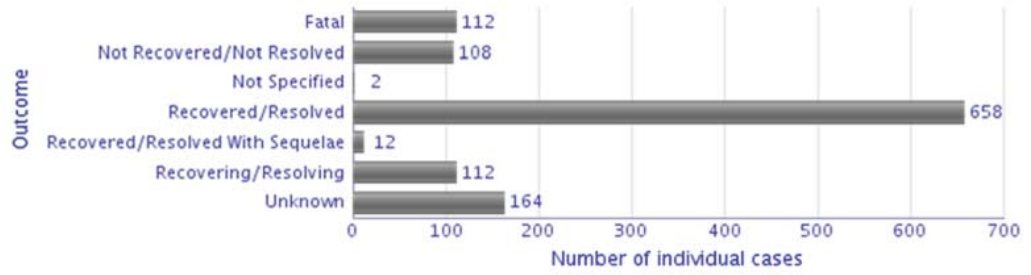
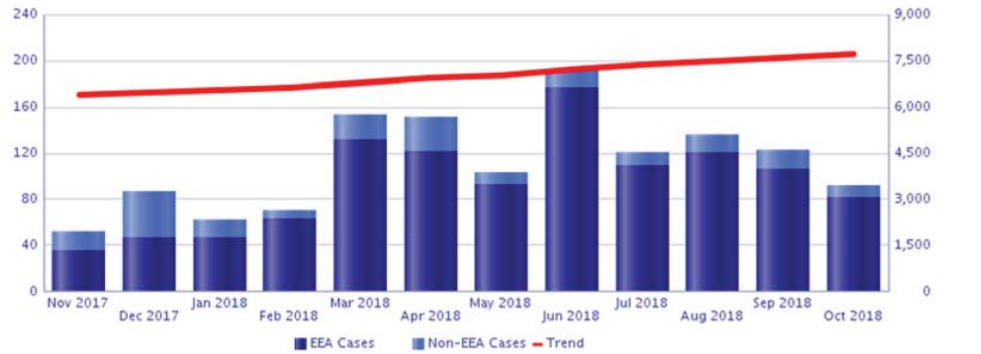


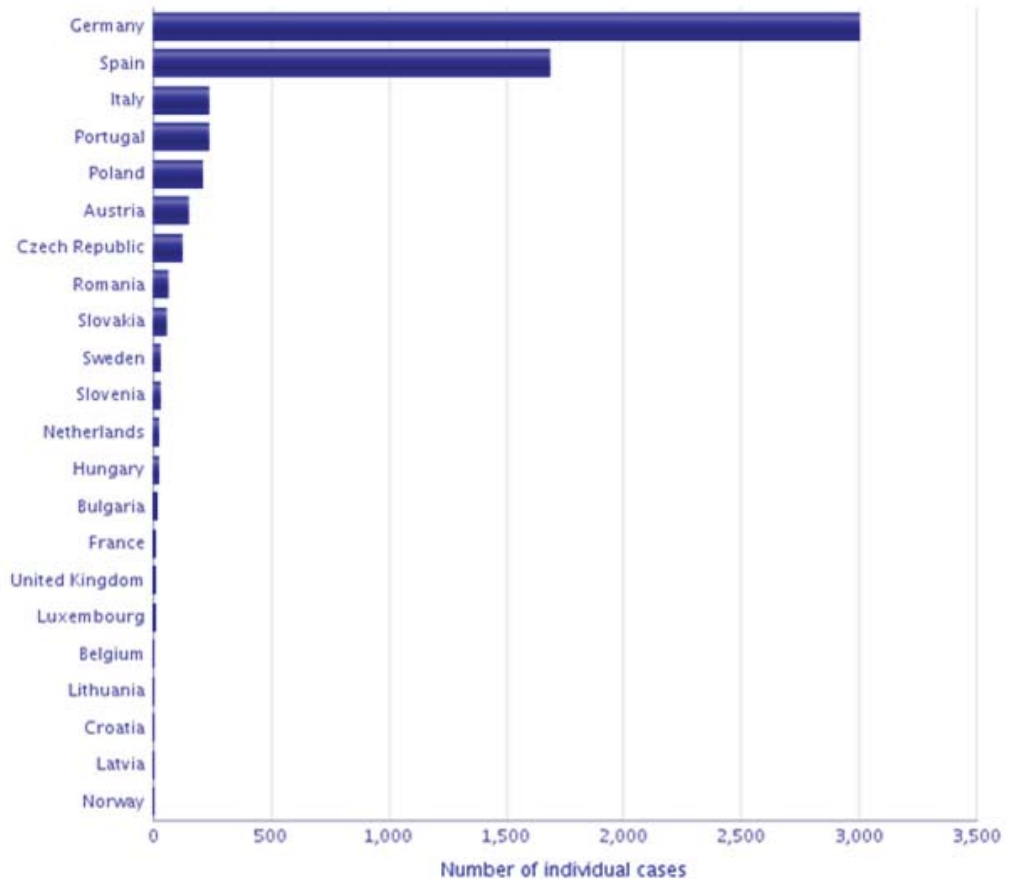
Figure 3. Number of individual cases of adverse effects of metamizole identified in EudraVigilance base in a period from November 2017 to October 2018



igilance base (<https://bi.ema.europa.eu/analyticsSOAP/saw.dll?PortalPages>), overall of 7711 adverse effects related to metamizole were reported so far (until October 2018).

Fifteen percent of these cases were reported as agranulocytosis. The most frequent appearance of agranulocytosis was registered in the age group from 18 to 64 years old (571 cases)

Figure 4. Distribution of metamizole adverse effects by the country in the European Economic Area reported up to October 2018



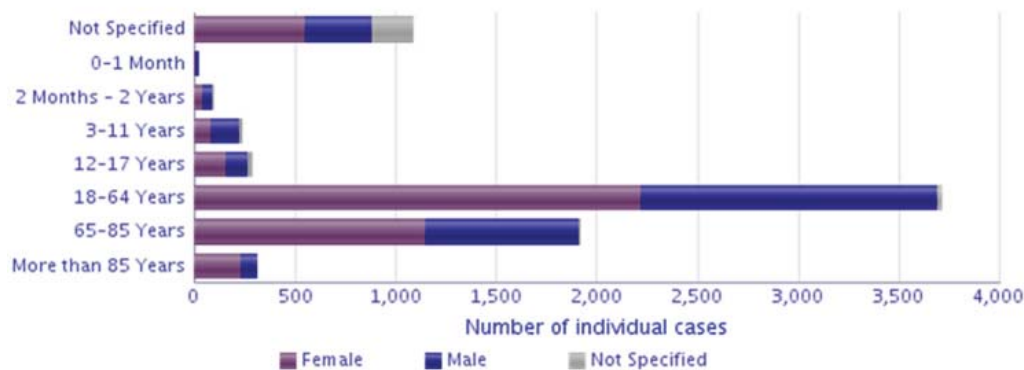


Figure 5. All individual reported cases of metamizole adverse effects classified by the age and gender of the patients

(Figure 1). That is the case with other adverse reactions to metamizole.

One hundred and twelve or 9.6% of 1162 cases of metamizole - induced agranulocytosis had fatal outcome (Figure 2). That means that 1.5% of overall adverse effects caused by metamizole had fatal outcome caused by agranulocytosis.

There is a trend (red line- cumulative number of metamizole adverse effects) of increasing reporting of adverse effects related to metamizole use in European countries during the last one-year (Figure 3).

Also there are differences between the countries from European Economic Area (EEA) and non-EEA. Significantly higher number of reported adverse effects was de-

tected in EEA (Figure 3). The reason for that might be in different politics of prescribing metamizole in these countries as well as different habits of the medical doctors and pharmacists in reporting of adverse reactions to drugs. The countries in which metamizole is the most frequently used analgesic for postoperative pain treatment are Germany and Spain [1, 14] and therefore most of its adverse effects have been reported there. Thirty nine percent of the total number of reported adverse reactions to metamizole in EEA occurred in Germany while 22% occurred in Spain (Figure 4).

Based on data from EudraVigilance, the difference between men and women in the frequency of reporting of overall metamizole induced adverse effects can be noticed i.e. they

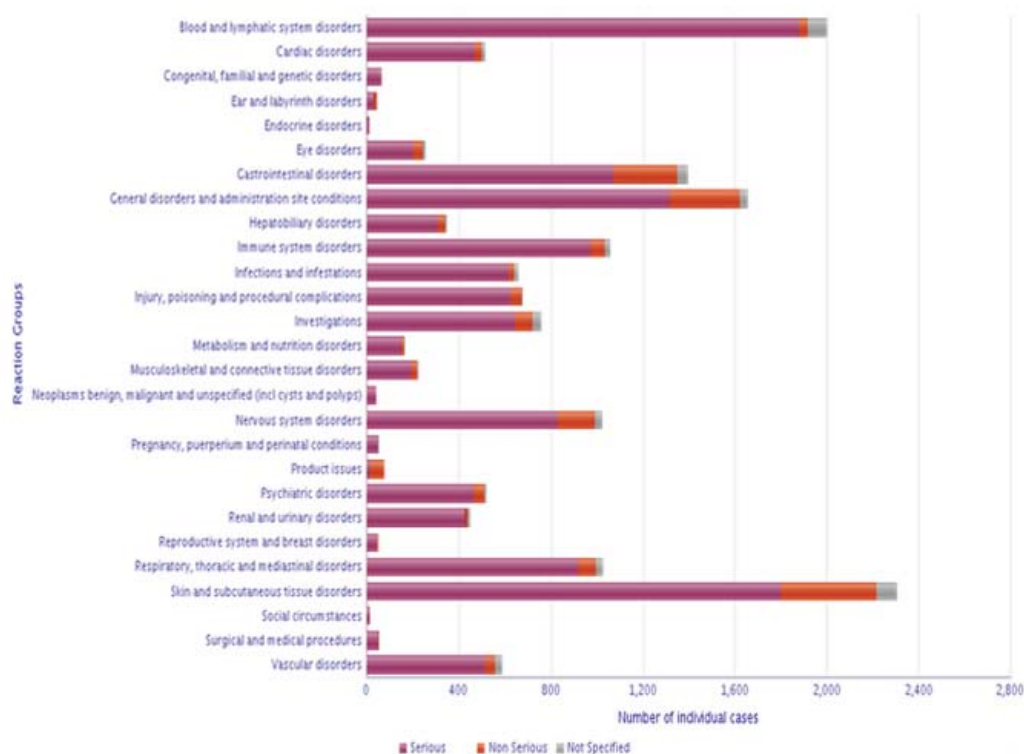
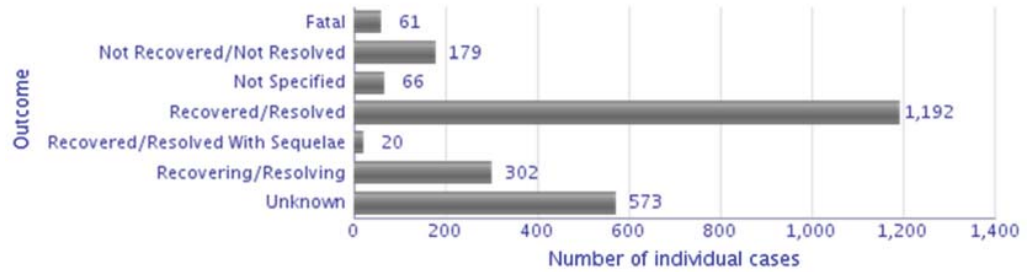


Figure 6. Structure of metamizole-related adverse reactions according to EudraVigilance [35]

Figure 7. Outcomes of skin and subcutaneous tissue disorders caused by metamizole



were more common in women than in men in all age groups (Figure 5). Also agranulocytosis is more common in women than in men (Figure 1).

The most common adverse reactions to metamizole, reported by Eudra Vigilance, were the skin and subcutaneous tissue disorders (30%) (Figure 6). The serious adverse effects manifested like skin and subcutaneous tissue disorders are toxic epidermal necrolysis. Sixty one of 2308 cases had fatal outcome (Figure 7).

The most serious adverse reactions to metamizole occurred within blood and lymphatic tissue disorders. About 94% of overall blood and lymphatic tissue disorders is estimated as serious (Figure 6).

Based on the data obtained from Medicines and Medical Devices Agency of Serbia (ALIMS) in the last five years, among 15 reported group of adverse reactions connected with metamizole skin and subcutaneous tissue disorders were present in 15 out of 50 reported cases (30%). Almost 40% of the

patients with recorded adverse reactions to metamizole belongs to age group from 18 to 44 year old, followed by 32% of registered patients, who are from 65 to 74 year old. Female gender accounted for 60% of patients with recorded adverse reactions to metamizole. Adverse reactions to metamizole reported during five year period, in our country, are presented in Table 1.

The skin and subcutaneous disorders reported during metamizole were skin rash, urticaria, morbilliform, scarlatiniform, erythematous, bullous, purpuric, exudative or fixed drug eruption, pemphigus vulgaris and toxic epidermal necrolysis [13]. Skin rash induced by metamizole use was described as mild [13]. The anaphylactic reaction has been reported when metamizole was used both parenterally and orally, but parenteral administration was associated with a higher risk of developing these reactions [2]. Pyrazolone-induced urticaria or angio-oedema can be a manifestation of a pseudoallergic reaction, produced by the inhibition of COX [13]. The most serious

Table 1. The overall number of adverse reactions to metamizole in a period from year 2013 to 2017 in Serbia

Adverse reaction	Number (%)
Gender male/female	2 / 13
Median age	36 (range 25-61)
Median neutrophil count nadir (range) $\times 10^9/l$	0.3 (range 0-0.5)
Median duration of agranulocytosis days	7 (4-15) days
recovery	14 (93.3%)
death	1 (6.6%)
Asymptomatic neutropenia	1 (6.6%)
Isolated fever	4 (26.6%)
Documented pneumonia	4 (26.6%)
Nonsystemic infections, sore throats and acute tonsillitis	5 (33.3%)
Normal	4 (26.6%)
Hypoplasia of granulocytic cells	5 (33.3%)
Hyperplasia of granulocytic cells	5 (33.3%)
Other abnormalities	1 (6.6%)
History of adverse drug reaction	3 (20.0%)
Infection preceding acute agranulocytosis	1 (6.6%)

life threatening cutaneous adverse effects are Stevens-Johnson's syndrome and toxic epidermal necrolysis (Lyell's syndrome).

Bronchospasm has also been described following administration of metamizole [2, 13]. Allergic reactions to metamizole can even provoke asthma attack.

Since metamizole is a strong COX-1 inhibitor, one would expect adverse effects like gastric or duodenal ulcers. However, they were not reported more often than it would be expected in contrast to other non-selective NSAIDs. Metamizole has been shown relatively safe for the stomach and the duodenum [33].

Due to its mentioned mechanism of action it would also be expected that metamizole use is associated with kidney problems, but, based on the available data, it is relatively safe for kidney function [33].

There are hardly any reports in the literature of metamizole overdose in humans. In the case of metamizole overdose nausea, vomiting, pain in the abdomen, kidney damage, hypotension, tachycardia, vertigo might occur [2]. Metamizole overdose was associated with mild, mainly gastrointestinal toxicity. After high dose metamizole intake red color of urine, resulted from the excretion of a rubazonic acid was reported [11]. Treatment should include symptomatic and supportive measures.

Availability of metamizole worldwide

There is a different policy regarding metamizole usage among different countries which is related to adverse reactions to metamizole, especially due to agranulocytosis. In many of them, including the United States of America, the United Kingdom and Japan, it is withdrawn from the market; in some of them (Italy, Belgium, the Netherlands, Germany, Spain), it is available only as a prescription drug for strictly defined indications, while in Mexico, Brazil and China it can be obtained as an Over-The-Counter or OTC drug [1,29].

The indication for the metamizole use also seems to differ considerably. It was synthesized by the German company Hoechst AG under brandname "Novalgin" in 1920, and its mass production started in 1922 [10]. Therefore, it is still one of the most frequently prescribed analgesics in Germany. Indications for metamizole prescribing are: pain due to

intestinal colic, postoperative pain, pain due to trauma, cancer pain and fever that is unresponsive to other measures [20].

In the Netherlands, it is only registered for *i.v.* use, and the indication for metamizole is short-term treatment of severe acute pain or high fever, if other drugs are contraindicated, or in case of high fever, when other methods have failed. These conditions are related to both adults and children [1]. In Spain, a survey of postoperative treatment in children showed that metamizole was one of the most frequently used analgesics [34]. Therefore, it is still used in some parts of Europe, as well as in South and Central America [1].

In Serbia, metamizole is a product licensed for short-term use in severe posttraumatic and postoperative pain, when therapy with other non-opioid analgesics is unsuccessful [2]. The available formulations are designed for oral, intravenous and intramuscular use. In Croatia, metamizole is marketingly authorized for the treatment of short-lasting severe pain of different origin (postoperative, posttraumatic, cancer pain, abdominal pain such as colic, and pain in other acute and chronic conditions), if other therapeutic interventions are insufficient [21].

CONCLUSION

Metamizole is still a stigmatized medication in various settings due to the reports of its relation to agranulocytosis. Despite this, its use is well-established in many countries where metamizole represents one of the most frequently used analgesics in postoperative pain management, both in adults and children, but also in other indications. Future randomized, controlled clinical trials should be organized with the aim of assessing its safety and efficacy, because the benefits of metamizole should be weighed against the risk of metamizole-induced adverse effects, especially in comparison with other NSAIDs. This is the only way of defining its place in the contemporary pharmacotherapy concerning pain management.

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Metamizol: aktuelno stanje bezbednosti i efikasnosti

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KRATAK SADRŽAJ

Metamizol je nesteroidni antiinflamatorni lek koji poseduje analgetsko, antipiretsko, spazmolitičko i slabo antiinflamatorno dejstvo. Smatra se da je analgetsko dejstvo metamizola zasnovano na inhibiciji enzima ciklooksigenaza i stimulaciji kanabinoidnih receptora. Njegova upotreba je i dalje kontroverzna zbog agranulocitoze, ozbiljnog neželjenog efekta, čiji nastanak može biti izazvan primenom ovog leka. U mnogim zemljama je njegova upotreba zabranjena, u nekim se može propisivati pod strogim indikacijama, dok je u nekim zemljama, kao što su Meksiko, Brazil, Kina, u bezreceptnom režimu prodaje. Najčešći neželjeni efekti metamizola se ispoljavaju na koži i potkožnom tkivu. Smatra se da ima sličnu efikasnost sa analgeticima koji se često koriste u terapiji umerenog i jakog postoperativnog bola.

Ključne reči: metamizol, neželjeni efekti, agranulocitoza, bol, efikasnost

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